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# $SnBr_4$-promoted Friedel–Crafts type dehydrative alkylation reaction of diarylmethanols with 2-naphthol derivatives

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## ABSTRACT

Tin(IV) bromide was found to act as an efficient Lewis acid catalyst for the Friedel–Crafts type dehydrative alkylation reaction of diarylmethanols with 2-naphthol derivatives under mild conditions. The effects of the substituents on the substrates were systematically evaluated, and the reaction could be applied to a variety of substrates by tuning the conditions depending on the electronic properties of the starting materials.

The alkylation of arenes with alkyl halides, promoted by a Lewis acid like $AlCl_3$, is commonly known as a Friedel–Crafts alkylation reaction[1] and is one of the most important methods for the formation of alkyl-substituted aromatic compounds. In the classical Friedel–Crafts reaction, the Lewis acid is used in stoichiometric amount with coproduction of a hydrogen halide, and significant amounts of salt residues are removed after workup. With the increasing concern for environmental issues, the development of more atom-economical and environmentally friendly protocols is highly desirable. Nevertheless, in recent years, the Friedel–Crafts type dehydrative alkylation reaction of alcohols has attracted much attention from synthetic chemists because of the difficult catalytic activation of the hydroxyl group due to its poor leaving ability. Moreover, improved protocols are of great interest because of their green chemistry nature: in fact, these reactions would ideally produce water as the sole byproduct. In 1986, Uemura and coworkers first reported the $TeCl_4$-catalyzed Friedel–Crafts alkylation of alcohols with arenes.[2] The other two pioneering investigations of the catalytic Friedel–Crafts alkylation of free alcohols by Fukuzawa et al. and by Shimizu et al. use $Sc(OTf)_3$[3] and $Mo(CO)_6$,[4] respectively, as catalyst. Since then, significant efforts have been directed towards the development of new synthetic methods for the direct substitution of alcohols using a catalytic amount of Brønsted or Lewis acids, and many useful methods have been described to date.[5,6] Because the use of 2-naphthol derivatives such as 2,2′-dihydroxy-1,1′-binaphthyl (BINOL)[7] and Betti base[8] has been successfully extended to asymmetric catalysis, we became interested in the Friedel–Crafts type dehydrative alkylation reactions of diarylmethanols with substituted 2-naphthols to produce a variety of diarylmethylated 2-naphthol derivatives. Although several methods have already been reported using various catalysts, such as metal triflates (e.g., La, Yb, Sc, and Hf triflate),[9] $H_2SO_4$,[10] $NbCl_5$,[11] $I_2$,[12] surfactant-type Brønsted acid,[13] amberlyst-15,[14] pentafluorophenylboronic acid,[15] and $NaHSO_4/SiO_2$,[16] the substrate scope has not been thoroughly investigated in previous studies.[17] Because the reaction proceeds through carbocation intermediates, it should be influenced by the electronic effects of the substituents. Thus, a systematic investigation of substituents on the substrates is highly desirable in order to evaluate their electronic and steric effects. Notably, tin(IV) bromide is known to serve as an efficient Lewis acid for the activation of carbonyl groups; for example, the Prins cyclization reaction of α-acetoxy ethers was successfully employed for the construction of a tetrahydropyran ring skeleton using a stoichiometric amount of tin(IV) bromide.[18,19] Thus, it was hypothesized that treatment of diarylmethanols with tin(IV) bromide would generate the corresponding carbocation intermediates, which by reaction with 2-naphthols would provide the target molecules. Herein, we report an efficient method for the Friedel–Crafts type dehydrative alkylation reaction of diarylmethanols with various 2-naphthols using a catalytic amount of $SnBr_4$, and we systematically evaluate the effect of substituents on this transformation.

In order to optimize the reaction conditions, at first, the solvent effect was examined by carrying out the Friedel–Crafts alkylation reaction of benzhydrol (**1a**) with 2-naphthol in the presence of

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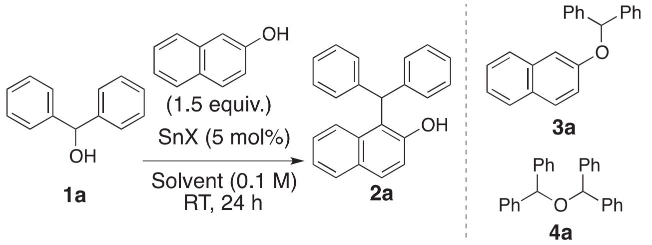
5 mol % $SnBr_4$, used as model system, in various organic solvents at room temperature for 24 h (Table 1). The reaction was not influenced by the polarity of the solvent and low or no reactivity was observed in oxygen-containing solvents, such as $Et_2O$, THF, EtOAc, and DMF (entries 3, 4, 7, and 9), probably because the oxygen atom coordinated to $SnBr_4$, thus reducing its catalytic activity. On the contrary, other solvents such as hexane, toluene, $CH_2Cl_2$, $(CH_2Cl)_2$, and MeCN, not containing oxygen atoms, were all effective in producing the desired product **2a** in good yields (entries 1, 2, 5, 6, and 8). Although the alkylation proceeded preferentially at the C-1 position rather than at the oxygen atom of 2-naphthol, the $^1H$ NMR spectrum of the crude reaction mixture showed a small amount of *O*-alkylated product **3a** and/or bis(diphenylmethyl) ether (**4a**), except when $CH_2Cl_2$ was used as the solvent. Upon increasing the catalyst loading to 30 mol %, the reaction was complete within 4 h to give **2a** in 95% yield (entry 10). We next examined other tin salts, such as $SnCl_2$, $SnCl_4$ and $SnBr_2$, in $CH_2Cl_2$. Interestingly, an appreciable amount of *O*-alkylated ether **3a** was obtained in the reaction using $SnCl_2$ and $SnCl_4$, although starting material **1a** was completely consumed and **2a** was obtained in good and moderate yields, respectively, (entries 11 and 12). In the case of $SnBr_2$, the reactivity was reduced as compared with the reaction with $SnBr_4$: **2a** was afforded in 81% yield along with a small amount of **3a** and **4a** and **1a** was recovered in 10% yield (entry 13).

After identifying the optimal solvent and catalyst, we surveyed the reaction of a series of diarylmethanols **1b–o** with 2-naphthol, to systematically explore the electronic and steric effects of the substituents on the aromatic rings of the substrates (Table 2). We examined the reactions of **1b–d** bearing methyl substituents at the *ortho*, *meta*, and *para* positions of the aromatic rings (entries 1–4). In entry 1, the desired **2b** was obtained in 87% yield along with 7% of *O*-alkylated ether **3b**; however, increasing the catalyst loading to 30 mol %, the yield of **2b** was improved to 96% (entry 2). On the contrary, the other two reactions proceeded smoothly to afford the desired **2c** and **2d** in good yields (entries 3 and 4). In addition, the reactions of **1e–g**, bearing methoxy substituents, were performed (entries 5–8). Substrate **1e** afforded the corresponding product in moderate yields, although the starting material was completely consumed (entry 5). The side products were not identified; however, because of the high reactivity of the diarylmethyl cation intermediate, several substitution reactions on the naphthol ring possibly occurred. The production of byproducts was relatively suppressed by decreasing the reaction temperature, to afford **2e** in 69% yield (entry 6). The reactions of **1f** and **1g** with substituents at the *meta* and *para* positions, respectively, afforded high yields of the desired products (entries 7 and 8). The reactivity of **1h–j**[20] containing electron-withdrawing groups showed a tendency similar to that of substrates bearing methyl substituents (entries 9–14). Almost no product was detected in the reactions of **1h** and **1i** using 5 mol % of $SnBr_4$ (entries 9 and 11); however, the reactivity was improved by increasing the catalyst loading to 110 mol % (entries 10, 12, and 13). On the contrary, the reaction of **1j** bearing *para* substituents was not affected and the corresponding product **2j** was afforded in good yields (entry 14). The reaction of **1k** and **1l** with naphthyl substituents and of **1m** with strong electron-donating groups proceeded smoothly to generate **2k–m** in good yields (entries 15–17). Substrate **1n**[20] containing an ethyl ester showed low reactivity; however, the yield of **2n** was improved by increasing the catalyst loading from 5 to 330 mol % (entries 18–20). Unfortunately, regardless of the catalyst loading, the reaction of **1o**[20] did not proceed at all and the starting material was recovered unchanged (entries 21 and 22). Presumably, because of the strong electron-withdrawing nature of the cyano group, the corresponding diarylmethyl cation intermediate could not be generated. It is noteworthy, however, that a variety

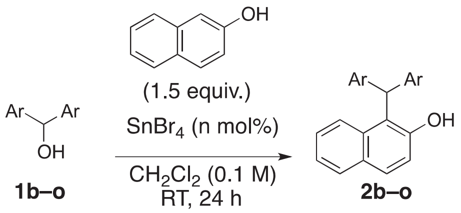
**Table 1**
Optimization of reaction conditions



| Entry | SnX | Solvent | Yield of **2a**[a] (%) | (**3a**; **4a**)[b] (%) |
|---|---|---|---|---|
| 1 | $SnBr_4$ | Hexane | 94 | (ND[c]; trace) |
| 2 | $SnBr_4$ | Toluene | 89 | (2; 4) |
| 3 | $SnBr_4$ | $Et_2O$ | 36 | (ND[c]; trace) |
| 4 | $SnBr_4$ | THF | NR[d] | (–; –) |
| 5 | $SnBr_4$ | $CH_2Cl_2$ | 96 | (ND[c]; ND[c]) |
| 6 | $SnBr_4$ | $(CH_2Cl)_2$ | 90 | (1; 4) |
| 7 | $SnBr_4$ | EtOAc | NR[d] | (–; –) |
| 8 | $SnBr_4$ | MeCN | 91 | (trace; 5) |
| 9 | $SnBr_4$ | DMF | NR[d] | (–; –) |
| 10[e] | $SnBr_4$ | $CH_2Cl_2$ | 95 | (ND[c]; ND[c]) |
| 11 | $SnCl_2$ | $CH_2Cl_2$ | 82 | (5; 8) |
| 12 | $SnCl_4$ | $CH_2Cl_2$ | 66 | (10; 13) |
| 13 | $SnBr_2$ | $CH_2Cl_2$ | 81 | (2; 2) |

[a] Isolated yield.
[b] Determined by $^1H$ NMR.
[c] Not detected.
[d] No reaction.
[e] The reaction was carried out by using 30 mol % of $SnBr_4$ for 4 h.

**Table 2**
Friedel–Crafts alkylation reaction of diarylmethanols with 2-naphthol



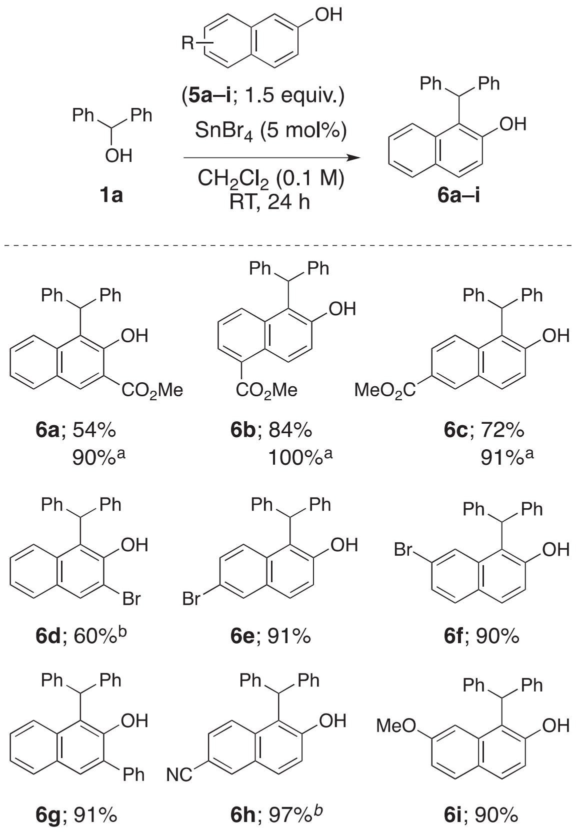
| Entry | Ar | *n* (mol %) | Yield[a] (%) |
|---|---|---|---|
| 1 | *o*-$MeC_6H_4$ (**1b**) | 5 | 87 (**2b**) |
| 2 | *o*-$MeC_6H_4$ (**1b**) | 30 | 96 (**2b**) |
| 3 | *m*-$MeC_6H_4$ (**1c**) | 5 | 89 (**2c**) |
| 4 | *p*-$MeC_6H_4$ (**1d**) | 5 | 92 (**2d**) |
| 5 | *o*-$MeOC_6H_4$ (**1e**) | 5 | 40 (**2e**) |
| 6[b] | *o*-$MeOC_6H_4$ (**1e**) | 5 | 69 (**2e**) |
| 7 | *m*-$MeOC_6H_4$ (**1f**) | 5 | 94 (**2f**) |
| 8 | *p*-$MeOC_6H_4$ (**1g**) | 5 | 87 (**2g**) |
| 9 | *o*-$ClC_6H_4$ (**1h**) | 5 | 3 (**2h**) |
| 10 | *o*-$ClC_6H_4$ (**1h**) | 110 | 79 (**2h**) |
| 11 | *m*-$ClC_6H_4$ (**1i**) | 5 | 1 (**2i**) |
| 12 | *m*-$ClC_6H_4$ (**1i**) | 30 | 41 (**2i**) |
| 13 | *m*-$ClC_6H_4$ (**1i**) | 110 | 83 (**2i**) |
| 14 | *p*-$ClC_6H_4$ (**1j**) | 5 | 86 (**2j**) |
| 15 | α-Np (**1k**) | 5 | 94 (**2k**) |
| 16 | β-Np (**1l**) | 5 | 89 (**2l**) |
| 17 | *p*-$Me_2NC_6H_4$ (**1m**) | 5 | 90 (**2m**) |
| 18 | *p*-$EtO_2CC_6H_4$ (**1n**) | 5 | NR[c] (**2n**) |
| 19 | *p*-$EtO_2CC_6H_4$ (**1n**) | 110 | 61 (**2n**) |
| 20 | *p*-$EtO_2CC_6H_4$ (**1n**) | 330 | 89 (**2n**) |
| 21 | *p*-$NCC_6H_4$ (**1o**) | 5 | NR[c] (**2o**) |
| 22 | *p*-$NCC_6H_4$ (**1o**) | 330 | NR[c] (**2o**) |

[a] Isolated yield.
[b] The reaction temperature was 0 °C.
[c] No reaction.

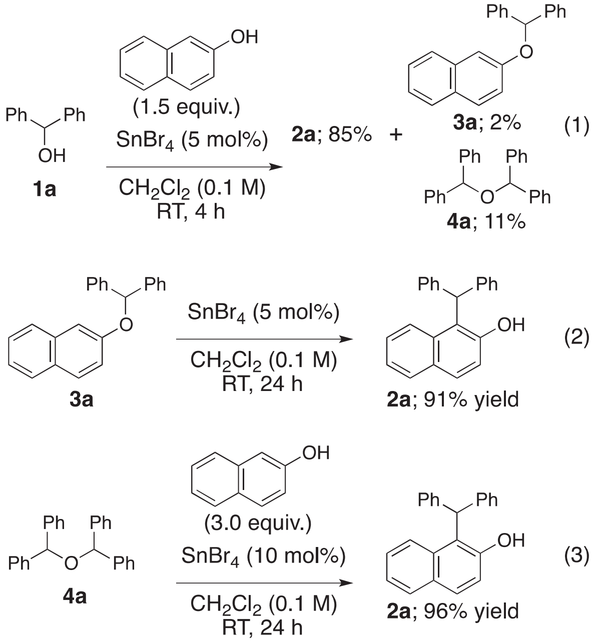
of diarylmethanols **1b**–**n** were viable for the present reaction, regardless of the nature of the functional groups on the aromatic rings.

Next, the reaction of benzhydrol (**1a**) was carried out with various 2-naphthol derivatives **5a**–**i**, in order to elucidate the scope and limitations under the optimized reaction conditions (Scheme 1). The reaction of compounds **5a**–**c** with an ethyl ester on the naphthyl ring, performed under the previously optimized conditions, that is, in the presence of 5 mol % of catalyst at room temperature for 24 h, generated the target molecules **6a**–**c** in moderate yields along with the formation of the bis(diphenylmethyl) ether (**4a**) as a byproduct. Upon increasing the catalyst loading to 30 mol %, **6a**–**c** were obtained in high yields and byproduct **4a** was not detected. On the other hand, the reaction of 6- and 7-bromo substituted 2-naphthol derivatives **5e** and **5f** gave good results using 5 mol % of SnBr$_4$; however, surprisingly, 3-bromo substituted 2-naphthol derivative **5d** afforded a moderate yield of the corresponding desired product, even upon increasing the catalyst loading. Several other 2-naphthols **5g**–**i** were examined and high yields were obtained regardless of the steric and electronic effects of the substituent groups on the naphthyl rings.

In order to identify the reaction intermediates, the reaction of **1a** with 2-naphthol catalyzed by 5 mol % of SnBr$_4$ was quenched after 4 h, and the desired compound **2a** was obtained in 85% yield along with 2% of *O*-alkylated product **3a** and 11% of ether **4a** as byproducts (Scheme 2, Eq. 1). Because the same transformation conducted for 24 h afforded **2a** as the sole product (Table 1, entry 5), we speculated that ethers **3a** and **4a** could be activated by SnBr$_4$ to regenerate the diphenylmethyl cation.[9,21,22] Thus, in order to confirm this hypothesis, ether **3a** was subjected to the above conditions in the absence of 2-naphthol and **2a** was produced in 91% yield (Scheme 2, Eq. 2). Similarly, the reaction of **4a** was conducted to afford **2a** in 96% yield (Scheme 2, Eq. 3). These results indicated that the reaction partially proceeds via ethers **3a** and **4a**.



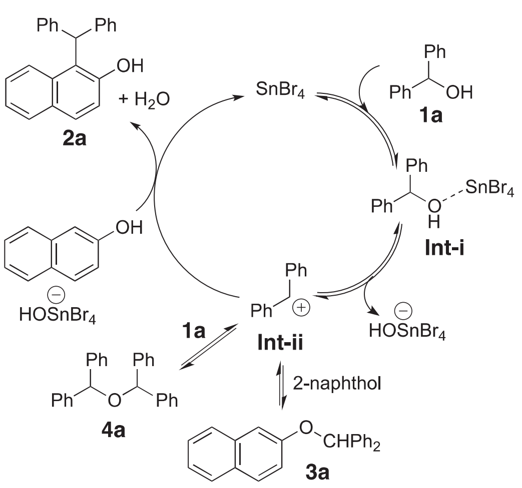
**Scheme 1.** Friedel–Crafts alkylation reaction of benzhydrol with substituted 2-naphthols. [a]Using 30 mol % of SnBr$_4$. [b]Using 110 mol % of SnBr$_4$.



**Scheme 2.** Examination of the reaction intermediates **3a** and **4a**.

A proposed catalytic pathway is illustrated in Scheme 3. At first, the hydroxyl oxygen of alcohol **1a** is activated upon coordination with SnBr$_4$, to generate diphenylmethyl cation **Int-ii** via **Int-i**. We suggest that **Int-ii** and ethers **3a** and **4a** are partially in equilibrium, that is, **Int-ii** reacts with 2-naphthol and **1a** to produce **3a** and **4a**, which are activated by SnBr$_4$ to regenerate **Int-ii**. Finally, the formed cation **Int-ii** reacts with 2-naphthol to afford the desired **2a** with dehydration and regeneration of the catalyst. On the other hand, for less reactive substrates with electron-withdrawing groups, stoichiometric amounts of catalysts are required.

In summary, we have developed an efficient Friedel–Crafts type dehydrative alkylation reaction of diarylmethanols with 2-naphthols promoted by SnBr$_4$ under mild conditions. Variously substituted substrates were applicable for this transformation by adjusting the catalyst loading and the reaction temperature according to the electronic nature of the substrates. Further studies



**Scheme 3.** Proposed catalytic reaction pathway.

are now in progress in our laboratory to expand the reaction scope and to develop novel chiral catalysts.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.064.

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